

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number  
WO 2004/050096 A3

(51) International Patent Classification<sup>7</sup>: A61K 31/66, 45/06, A61P 35/00, 37/00, 35/04

(21) International Application Number:  
PCT/IB2003/006375

(22) International Filing Date: 2 December 2003 (02.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
02292963.2 2 December 2002 (02.12.2002) EP

(71) Applicant (for all designated States except US): INNATE PHARMA [FR/FR]; Immeuble Grand Pré, 121, ancien Chemin de Cassis, F-13009 Marseille (FR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ROMAGNE, François [FR/FR]; Bat. A3, Les Hauts de Fontaine, F-13600 La Ciotat (FR). SICARD, Hélène [FR/FR]; 19 Beauvallon Centre, F-13009 Marseille (FR). TIOILLIER, Jérôme [FR/FR]; 17 rue Bienvenu, F-13008 Marseille (FR). BELMANT, Christian [FR/FR]; 36 Impasse du Hameau de la Tour, F-83140 Six-Fours-Les-Plages (FR).

(74) Agents: BECKER, Philippe et al.; Cabinet Becker et Associés, 35, rue des Mathurins, F-75008 Paris (FR).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- of inventorship (Rule 4.17(iv)) for US only
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
16 September 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/050096 A3

(54) Title: PHOSPHOANTIGENS FOR REGULATING AN IMMUNE RESPONSE

(57) Abstract: The present invention relates to compositions and methods for regulating an immune response in a subject, particularly to treat a subject with a tumor, notably a solid tumor, or an infectious disease. Disclosed are methods of regulating the innate immunity in a subject, such as by regulating the activity of  $\gamma\delta$  T cells in a subject. Disclosed are combinations of a cytokine (IL-2) and a  $\gamma\delta$  T cell activator, particular administration regimens and dosages can produce a remarkable expansion of  $\gamma\delta$  T cells in vivo and a remarkable increase in a subject's immune defense. Preferred  $\gamma\delta$  T cell activators include BrHPP (Bromohydrin PyroPhosphate or Phosphostim), CBrHPP, HDMAAPP, CHDMAAPP and Epox-PP.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/06375

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/66 A61K45/06 A61P35/00 A61P37/00 A61P35/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, COMPENDEX, EMBASE, BIOSIS, SCISEARCH, PASCAL, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/142996 A1 (GREEN JONATHAN ET AL) 3 October 2002 (2002-10-03) abstract; figures 1-3; example 5 paragraphs '0009!, '0050!, '0052!	1-8, 16-21
X	WO 00/59916 A (BELMANT CHRISTIAN ; INST NAT SANTE RECH MED (FR); BONNEVILLE MARC (FR)) 12 October 2000 (2000-10-12) cited in the application page 17, line 21 - line 25; example 14; tables I,II	49, 57-72, 74-77
X	WO 00/12519 A (BELMANT CHRISTIAN ; INST NAT SANTE RECH MED (FR); PEYRAT MARIE ALIX (F) 9 March 2000 (2000-03-09) cited in the application page 21, line 19 - line 23	1,2,26, 27,30,73

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

15 April 2004

Date of mailing of the international search report

06. 07. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Laffargue-Haak, T

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/06375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 03/009855 A (JOMAA PHARMAKA GMBH ; REICHENBERG ARMIN (DE); EBERL MATHIAS (DE); WOLF) 6 February 2003 (2003-02-06) cited in the application * p. 10, compounds 15 (=CHDMAPP) and 17 (=HDMAPP) * page 13, line 8 - line 31; claims 1-42	1,2,26, 40-42, 50,51,78
X	KUNZMANN VOLKER ET AL: "Stimulation of gammadelta T cells by aminobisphosphonates and induction of antiplasma cell activity in multiple myeloma" BLOOD, vol. 96, no. 2, 15 July 2000 (2000-07-15), pages 384-392, XP002276947 & ISSN: 0006-4971 cited in the application * p. 389, Cytoreductive effects of IPP and pamidronate in multiple myeloma * * p. 389, Antiplasma cell activity by pamidronate * abstract; table 1	1,16-20, 25,26, 40,73
P,X	WILHELM MARTIN ET AL: "gammadelta T cells for immune therapy of patients with lymphoid malignancies." BLOOD, vol. 102, no. 1, 1 July 2003 (2003-07-01), pages 200-206, XP002276948 & ISSN: 0006-4971 abstract; figures 2,3; tables 1,5	1,2, 57-65, 67,68, 71-77
P,X	DATABASE PROMT 15 December 2003 (2003-12-15), XP002276950 retrieved from STN Database accession no. 2003:627750 abstract & "Phosphostim Innate Pharma partnering opportunity, Worldwide (solid tumor) Innate Pharma phase change I, France (solid tumor)" R D FOCUS DRUG NEWS, 2003,	1,2, 16-28, 49,73
X	DATABASE PHIN 8 March 2002 (2002-03-08), XP002276951 retrieved from STN Database accession no. :2002:6085 abstract & ANONYMOUS: "Innate gets Euros2 million loan from French agency" SCRIP, no. 2727, 8 March 2002 (2002-03-08), page 7,	1,2, 16-28, 49,73

-/-

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/06375

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CBNB "Innate Pharma exceeds objectives in obtaining funding for first clinical trials."</p> <p>XP002276952</p> <p>retrieved from STN</p> <p>Database accession no. 19(9):12851</p> <p>abstract</p> <p>&amp; PHARMACHEM (NOV-DEC 2002) 1 (11-12), 76</p> <p>AVAILABILITY: B5 SRL. VIA CESARE DA SESTO, 10-20123 MILAN, ITALY. TEL. +39 02 83241119. FAX. + 39 02 8376457. WEB SITE WWW.B5SRL.COM., 2002,</p> <p>-----</p>	1,2, 16-28, 49,73
T	<p>MONTALVETTI ANDREA ET AL: "Farnesyl pyrophosphate synthase is an essential enzyme in <i>Trypanosoma brucei</i>: In vitro RNA interference and in vivo inhibition studies"</p> <p>J. BIOL. CHEM.; JOURNAL OF BIOLOGICAL CHEMISTRY MAY 9 2003,</p> <p>vol. 278, no. 19, 9 May 2003 (2003-05-09),</p> <p>pages 17075-17083, XP002276949</p> <p>*Fig. 1, Formula 10 phosphostim *</p> <p>-----</p>	1-79

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 03/06375

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Although independent claims 2, 58 and 59 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple Inventions in this International application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/ IB 03 /06375

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

#### Continuation of Box I.1

Although independent claims 2, 58 and 59 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

-----

#### Continuation of Box I.2

Claims Nos.: -

Present claims 1-79 relate to an extremely large number of possible compounds and uses. In fact, both the compounds ("gamma delta T cell activator") and their medical use ("for regulating the activity of gamma delta T cells") are functionally defined.

The search has been limited on the the following groups of gamma delta T cell activators : aminobisphosphonates and phosphoantigen compositions according to formula I to XVII, as defined in the description. As to the medical uses, the search has been limited to clearly defined medical indications, namely the treatment of tumors, in particular solid tumors, allergic diseases, autoimmune diseases and infectious diseases.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/06375

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 2002142996	A1 03-10-2002	AU 5214100	A 12-12-2000	
		BR 0010808	A 27-08-2002	
		CA 2374049	A1 30-11-2000	
		EP 1178810	A2 13-02-2002	
		JP 2003500352	T 07-01-2003	
		NO 20015638	A 15-01-2002	
		NZ 515541	A 28-03-2003	
		PL 351674	A1 19-05-2003	
		SK 16682001	A3 04-04-2002	
		CN 1384749	T 11-12-2002	
		WO 0071104	A2 30-11-2000	
		HU 0201329	A2 28-08-2002	
		ZA 200109556	A 06-11-2002	
WO 0059916	A 12-10-2000	FR 2791981	A1 13-10-2000	
		AT 258182	T 15-02-2004	
		AU 3823800	A 23-10-2000	
		DE 60007847	D1 26-02-2004	
		EP 1165573	A1 02-01-2002	
		WO 0059916	A1 12-10-2000	
		US 2004006131	A1 08-01-2004	
		US 2004009123	A1 15-01-2004	
		US 6624151	B1 23-09-2003	
WO 0012519	A 09-03-2000	FR 2782722	A1 03-03-2000	
		AT 227296	T 15-11-2002	
		AU 5426599	A 21-03-2000	
		CA 2341578	A1 09-03-2000	
		DE 69903838	D1 12-12-2002	
		DE 69903838	T2 10-07-2003	
		DK 1109818	T3 03-03-2003	
		EP 1109818	A1 27-06-2001	
		ES 2187184	T3 16-05-2003	
		WO 0012519	A1 09-03-2000	
		JP 2002523515	T 30-07-2002	
		PT 1109818	T 28-02-2003	
WO 03009855	A 06-02-2003	DE 10134705	A1 06-02-2003	
		DE 10135395	A1 13-02-2003	
		CA 2453817	A1 06-02-2003	
		WO 03009855	A2 06-02-2003	
		EP 1408984	A2 21-04-2004	